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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/580,173	05/22/2006	Stefano Turchetta	622-95	4021

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EXAMINER	
MORRIS, PATRICIA L	
ART UNIT	PAPER NUMBER
1625	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/580,173	TURCHETTA ET AL.	
	Examiner	Art Unit	
	Patricia L. Morris	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 July 2009 and 08 July 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *34-37,39-50,52-55 and 77-94* is/are pending in the application.

4a) Of the above claim(s) *39-46,57-76 and 89-94* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34-37,47-50,52-55 and 77-88* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/8/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 34-37, 47-50, 52-55 and 77-88 are under consideration in this application.

Claims 39-46, 57-76 and 89-94 are held withdrawn from consideration as being drawn to nonelected subject matter 37 CFR 1.142(b).

Election/Restrictions

The restriction requirement is deemed sound and proper and is hereby made final.

Specification

Content of Specification

(h) Brief Description of the Several Views of the Drawing(s): See MPEP § 608.01(f). A reference to and brief description of the drawing(s) as set forth in 37 CFR 1.74.

The disclosure is objected to because of the following informalities: The specification fails to recite a brief description of the drawings. A

Appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 34-37, 47-50, 52-55 and 77-88 are rejected under 35 U.S.C. 102(b) as being anticipated by Grunenberg et. al. for the reasons set forth in the previous Office action.

Again, Grunenberg et al. specifically disclose the instant compound. Note examples 1-3 of Grunenberg et al. The prior art's pharmaceutical composition comprising the instant compound would be the same as the instant compositions comprising form I, since form I would

no longer exist in solution, or after granulation, compaction or tableting process, as it is well known in the art that such process(es) would lead to alteration of the crystal structure. Note, for example, Chemical & Engineering News, pages 33-34. It is well known in the art that the forms would lose their unique crystalline structure especially in solutions.

Contra to applicants' arguments in the instant response, a novel chemical product is identified first by its "chemical nature", i.e. elemental and atom content. It is a well known fact that many pharmaceutical solids exhibit polymorphism which is frequently defined as the ability of a substance to exist as two or more crystalline phases that have different arrangements and/or conformations of the molecules in the crystal lattice. See US Pharmacopia or Muzaffar et al. Thus *in the strictest sense, polymorphs are different crystalline forms of the* ***same pure substance*** *in which the molecules have different arrangements and/or different conformations of the molecules*. See Brittain p. 1-2.

Applicants have failed to present any single X-ray crystal diffraction of the instant compound and compositions *vis-à-vis* the prior art *anhydrous* compounds at the same radiation parameters. Applicants' claims are drawn solely to an *anhydrous form.* Applicants allege that the X-ray diffraction pattern of Grunenberg et al. is substantially different from the X-ray diffraction pattern disclosed herein. As it has been clearly delineated supra that there is insufficient basis for discerning what is the chemical identity of the instant claims.

Instant	'752 table 2 anhydrous form
5.815	5.8
8.575	8.6
10.335	10.3
14.535	14.5
15.185	15.0
17.335	17.5
19.315	19.3

19.760	19.6
21.640	21.5
23.160	23.0

At least 10 peaks are found to be within the ±0.2θ of the '752 material. It is well recognized in the chemical art that for every measurement, there is a margin of allowable error, that is within such margin the numbers are considered the same. For powdered diffraction 2 theta, the Brittain reference on page 236 employs the US Pharmacopeia handbook value of ±0.2θ.

The declaration of Turchetta, while interesting, is of little if any probative value because it fails to provide a single crystal comparison of the instant compound and the prior art anhydrous compound at the same radiation parameters. Note figure 4.21 on page 118 of Bernstein wherein the same compound shows two different X-ray patterns. Further, Davidovich et al. on page 16, states that changes in powder X-ray powder often resulted from experimental artifacts rather than polymorphism and that most of these changes were due to particle size/morphology, sample holder/preparation, and instrument geometry.

As for the method of using the form A for treating bacterial infections, applicants provided no arguments or evidence that the form I of the claims will not be identical to the prior art compound because *"when a crystalline solid is dissolved in solvent, the crystalline structure is lost so that different polymorphs of the same substance will show the same absorption spectra as solution"* (see Jain p.316). Nor did applicants showing any deviation of parameters that the form will not behave in the same physiological manner as all other drugs as delineated by textbook of pharmacology (see Rowland and Tozer p.123).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 34-37, 47-50, 52-55 and 77-88 are rejected under 35 U.S.C. 103(a) as being unpatentable over the teachings of Grunenberg et al. in view of Chemical & Engineering News, , Brittain et al., US Pharmacopia, , Muzaffar et al., Jain et al., Taday et al. and Concise Encyclopedia Chemistry for the reasons set forth in the previous Office action.

Contra to applicants' assertions in the instant response, one having ordinary skill in the art would find the claims prima facie obvious because the instant claims differ from the known product merely by forms and the physical properties innate to the forms. It is well recognized in the pharmaceutical field that many solids including the instant compound exhibits polymorphism which is the innate nature of the particular drug (see US Pharmacopia #23, national formulary #18). It is also well recognized in the art that the innately existing different "morph" will display

different physical properties such as X-ray diffraction, melting point etc. (see Brittain p. 178-179, 219). As clearly stated by Brittain (p. 1-2) supra, as well as set forth by the court in In re Cofer (CCPA 1966) 354 F2d 664, 148 USPQ 268, ex parte Hartop 139 USPQ 525, that a product which is merely a different form of a known compound, notwithstanding that some desirable results are obtained therefrom, is unpatentable. The instant claims are drawn to the ***same pure substance*** as the prior art that only have *different arrangements and/or different conformations of the molecule*. A mere difference in a physical property is a well known conventional variation for the same pure substance is *prima facie* obvious. Mere difference in physical property is a well known conventional variation for the same pure substance (see Brittain p.1-2), *i.e.,* prima facie obvious. For a known compound with defined chemical nature to be patentably for a new form, it must have a patentability basis of an advantage in terms of stability, formulation, solubility, bioavailability, ease of purification, preparation or synthesis, hygroscopicity, recovery or prevention of precipitation, etc., (see Brittain p. 185). Even if the product of the instant application and the prior art differ in X-ray diffraction or "form", the mere difference in physical parameter such as X-ray diffraction pattern does not offer any unexpected advantage of the prior art product with the same chemical and biological properties, *i.e.,* a mere variation in physical property which flows naturally with the changing form.

The Declaration of Turchetta attempts to show that instant form A is more soluble than the monohydrate moxifloxacin hydrochloride in the prior art. However, the instant claims recite an anhydrous form A. The declaration fails to compare the instant form A with the closest prior art compound, *i.e., the anhydrous form.*

Claim Rejections - 35 USC э 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 77-88 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

No support can be found anywhere in the specification for the compounds, compositions and methods using the compound in tablet form. The specification is silent as to any X-ray diffraction spectrum, C13 NMR or IR spectrums of the compound or composition in tablet form. Example 6 fails to support all tablets having the recited X-ray diffraction pattern, etc. The specification only discloses the above noted spectrum for the crystalline form only.

Claims 47-50, 52-55 and 77-88 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement as well as failing to comply with the enablement requirement. The claim contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention, or was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention and maintained for the reasons of record.

Applicants have failed to argue this rejection or provide any objective evidence that the instant polymorph is indeed maintained in the compositions. Applicants have provided no objective evidence that the instant polymorph will not be identical to the prior art compounds because "*when a crystalline solid is dissolved in solvent, the crystalline structure is lost so that different polymorphs of the same substance will show the same absorption spectra as solution*" (see Jain p. 316). It is well recognized in the art that for a given crystalline form of a drug, *in absence of explicit* enabling description, in view of the high degree of unpredictability, even if one is in possession of a particular crystalline form, no predictability can be found that such forms will prevail in pharmaceutical compositions. See Chemical & Engineering News.

Again, no where in the specification is a composition of "the particular XRD" of the claimed form is described or made, that is the composition contains the material having the XRD peaks recited in claim 34.

In evaluation of possession, it was clearly provided to applicants that:

--a complete review of the state of the art with many references indicating the necessity of explicit and specific guidance for preparing pharmaceutical composition maintaining crystallinity of the active agent;

The state of the pharmaceutical composition containing polymorphic form art provided per ponderous of evidence that *unless specific and particular* conditions can be obtained, the formulation process would cause polymorphic forms to change.

See :

--Muzaffar et al. p.60 "At any one temperature and pressure only one crystal form of a drug is stable and any other polymorph existing under these conditions will convert to the stable form .... " And p.63-65 (a)-(h) pharmaceutical preparing processes affect polymorphism;

--Jain et al. p.322-326, manufacturing processes that affect polymorphs ;

--Doelker et al., 2002 abstract, "One may also observe changes in technology or pharmaceutical properties that are due to polymorphic environmental conditions undergone by the product or the dosage form"

--Doelker et al. 1999 (already of record) abstract "...a given drug, although chem. well defined, may exhibits quite different behavior. Process conditions (grinding, tableting, granulations, drying) may also affect secondary properties of the drug, such as compactibility, wetttability, solvent, dissolution rate, bioavailability and even pharmacological, activity."

--Otsuka et al. p.852 ...in formulation studies and the method preparing CBZ has been shown to affect the drug's pharmaceutical properties through the polymorphic phase transformation of the bulk CBZ powder during the manufacturing process"

Taday et al. p. 831 states "Once in the desired crystalline form, the polymorphis state *may be changed* by incorrect storgage or even during tablet preparation and p. 836, figure 8, wherein compound of four form in pharmaceutical composition resulted in similar spectra, *i.e.,* form.

The pharmaceutical composition field has well recognized that stability of an active principle i.e. specific polymorphic form of a compound, has no predictability on its outcome in composition processing. It is known in the art that:

--Singhal et al. "..It should be pointed out that a major portion of any formulation effort is the choice of exipients and processes which minimize the chemical instability of the drug...." P.338, left col.

--CMU phar. Polymorph. "there are a number of examples in which polymorphic molecules change crystal structure under processing conditions while in contact with liquids or solid material. In these enviroments, it is difficult to apply standard techniques to identify the predict the transformation...." See p.1-2 para.

--US 6,627,646, col. 1-2, especially, "..from thermodynamic considerations only one polymorph will be stable;.....however, thermodynamic stability is not sufficient to ensure that the stable polymorph will always be produced.....most transformations occur in suspension and are solvent mediated.....other transformations are irreversible over a broad range of temperature:

-- the specification fails to disclose any carrier that retains the crystallinity of the compound;

--a complete review of the skill level of artisan in the field providing that the field is well aware of preserving crystallinity proper solid carrier, proper compression condition, etc. must provided for such composition to be available (see Muzaffar, Jain, Doelker or Otsuka et al. provided;

--a complete review of the unpredictability and empirical nature of the art and the lack of any preparation of any crystalline form being disclosed in the specification.

The Office has met the burden of establishing a prima facie case of lacking sufficient description based on the complete review of the specification in view of the state of the art. In evaluation of enablement, it was clearly delineated that the specification is silent as to what specific excipients and preparation conditions are employed to form the composition containing the specific form C well before the formulation is even administered to a patient.

In terms of the 8 Wands factors, undue experimentation would be required to make or use the invention based on the content of the disclosure due to the breadth of the claims, the level of unpredictability in the art of the invention, and the poor amount of direction provided by applicants. Taking the above factors into consideration, it is not seen where the instant claim is enabled by the instant application.

In view of the per ponderous of evidence as delineated supra, it is evidenced that a crystalline drug does not automatically keeps its form in the pharmaceutical composition, thus *absent of any description or enablement* from the specification, enablement for the claimed composition and use is lacking.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 77-88 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 77-84 are indefinite because it is unclear how a crystalline compound by itself can be formed and maintained in a tablet without any inert ingredients. Further, claims 85-88 fail to recite the inert excipients present in the pharmaceutical compositions.

The claims measure the invention. United Carbon Co. V. Binney & Smith Co., 55 USPQ 381 at 384, col. 1, end of 1st paragraph, Supreme Court of the United States (1942).

The C.C.P.A. in 1978 held "that invention is the subject matter defined by the claims submitted by the applicant. We have consistently held that no applicant should have limitations of the specification read into a claim where no express statement of the limitation is included in the claim": In re Priest, 199 USPQ 11, at 15.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia L. Morris whose telephone number is (571) 272-0688. The examiner can normally be reached on Mondays through Fridays.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Patricia L. Morris/
Primary Examiner, Art Unit 1625

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October 26, 2009